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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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909 7590 09/01/2005

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EXAMINER	
BLANCHARD, DAVID J	

ART UNIT	PAPER NUMBER
1643	

DATE MAILED: 09/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/058,069	BRASLAWSKY ET AL.	
	Examiner	Art Unit	
	David J. Blanchard	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20,29,38-40,55-57,62,63,68-70 and 75-92* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20,29,38-40,55-57,62,63,68-70 and 75-92* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Exhibits A-B*.

DETAILED ACTION

1. Claims 1-19, 21-28, 30-37, 41-54, 58-61, 64-67 and 71-74 are cancelled.

Claims 20, 29, 55, 68 and 75 have been amended.

Claims 80-92 have been added.

2. Claims 20, 29, 38-40, 55-57, 62-63, 68-70 and 75-92 are pending and under examination.

3. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

4. This Office Action contains New Grounds of Rejections.

Rejections Withdrawn

5. All rejections set forth in the previous Office Action mailed 5/12/2005 are withdrawn in view of the amendments to the claims.

New Grounds of Rejections

6. Claims 20, 29, 38-40, 55-57, 62-63, 68-70, 75-92 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 20, 29, 38-40, 55-57, 62-63, 68-70, 75-92 are indefinite in the recitation of "a tetravalent antibody dimer..." that "has two antigen-binding sites" in claims 20, 29, 80 and 85. Does the tetravalent antibody dimer have two antigen-binding sites or four antigen-binding sites?

b. Claims 55, 68 and 81 are indefinite for reciting "wherein said antibody dimer is a chimeric antibody...". The claims are dependent upon base claims 20, 29 and 80, which recite that the antibody dimer comprises the CC49 humanized VH and VL sequences, comprising human frameworks and murine CDRs. The art indicates that a chimeric antibody comprises murine variable regions and human constant regions (see WO 00/26394, page 8). Is the "chimeric antibody" of claims 55, 68 and 81 a "chimeric antibody" in that it comprises murine variable regions and human constant regions as recognized in the art or are the variable regions chimeric in that they contain alternating human and murine sequences? Where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). In the instant case, the term "chimeric antibody" recited in claims 55, 68 and 81 has not been clearly redefined by the specification as containing the CC49 humanized VH and VL sequences (SEQ ID Nos:7 and 9, respectively) as required by the claims.

7. Claims 20, 29, 38-40, 55, 57, 62-63, 68, 70, 75-81, 83-92 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a dimeric antibody and a kit comprising said dimeric antibody comprising two antibodies that are non-covalently associated to form a tetravalent antibody dimer wherein each

antibody in the dimer comprises two heavy chain variable regions (SEQ ID NO:7) and two light chain variable regions (SEQ ID NO:9) and wherein the CH2 domain is deleted or wherein the CH3 domain may be fused directly to the hinge region, does not reasonably provide enablement for a dimeric antibody and a kit comprising said dimeric antibody comprising two antibodies that are non-covalently associated to form a tetravalent antibody dimer wherein each antibody in the dimer comprises two heavy chain variable regions (SEQ ID NO:7) and two light chain variable regions (SEQ ID NO:9) and wherein the CH2 domain is deleted and replaced with an amino acid spacer. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 1 12, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention is engineered antibodies wherein the relative skill of those in the art is deemed to be high. The claims broadly encompass dimeric antibodies and kits comprising such wherein the dimeric antibody comprises two antibodies that are non-covalently associated to form a tetravalent antibody dimer

wherein each antibody in the dimer comprises two heavy chain variable regions and two light chain variable regions and wherein the CH2 domain is deleted or the CH3 domain is fused directly to the hinge region or the CH2 domain replaced with an amino acid spacer as well as conjugates of said dimeric antibody comprising a cytotoxic agent.

The teachings in the specification are limited with respect to the broad scope of the claims. The specification only teaches dimeric antibodies wherein the CH2 domain is deleted and the CH3 domain is fused directly to the hinge region (see examples). The specification teaches that the deletion of the CH2 domain results in a bivalent molecule having a disulfide linked hinge region and mismatched CH3 domains, which are thought to align and interact non-covalently to provide stable tetravalent antibodies (see page 7). The specification does not teach dimeric antibodies comprising two antibodies that are non-covalently associated wherein the CH2 domain is replaced with an amino acid spacer. There are no working examples present in the specification to assist the skilled artisan in producing and using a dimeric antibody comprising two antibodies that are non-covalently associated wherein the CH2 domain is replaced with an amino acid spacer.

The state of the prior art indicates that producing dimeric antibodies comprising two antibodies that are non-covalently associated wherein the CH2 domain is replaced with an amino acid spacer is unpredictable. As pointed out by applicant in the response filed 7/11/05, Slavin-Chiorini et al (Cancer Biotherapy and Radiopharmaceuticals, 12(5):305- 316, 1997, cited previously) teach that chimeric CC49 antibodies in which the CH2 domains are replaced with a 10-residue glycine/serine spacer do not associate

non-covalently to form tetravalent dimeric antibodies (see Figure 3, page 309 and applicant's response filed 7/11/05, page 10). Further, as acknowledged by applicant, and consistent with the teachings of Slavin-Chiorini et al, the present application describes anti-TAG-72 antibodies in which the CH2 domains are deleted and replaced with a 10-residue glycine-serine spacer do not associate non-covalently to form tetravalent, dimeric antibody complexes (see page 25, lines 23-24). The HPLC sizing data in Figure 9 of the present application shows that chimeric CH2 domain-deleted CC49 antibodies associate non-covalently to form tetravalent, dimeric antibody complexes and elute from a sizing HPLC column in two clearly defined peaks, whereas chimeric CC49 antibodies in which the CH2 domains are replaced with a glycine/serine spacer elute as a single peak, which indicates that they do not associate non-covalently to form dimeric antibody complexes (see applicants response 7/11/05, page 10).

There is insufficient evidence or nexus that would lead the skilled artisan to predict the ability to produce antibodies in which the CH2 domains are deleted and replaced with a 10-residue glycine-serine spacer, wherein the antibodies non-covalently associate to form tetravalent, dimeric antibody complexes. The specification does not teach how to extrapolate data obtained from chimeric CH2 domain-deleted CC49 antibodies which associate non-covalently to form tetravalent, dimeric antibody complexes to the development of CH2 domain-deleted antibodies in which the CH2 domain is replaced with an amino acid spacer wherein the antibodies associate non-covalently to form tetravalent, dimeric antibody complexes.

In view of the lack of the predictability of the art to which the invention pertains, the lack guidance and direction as it pertains to CH2 domain-deleted antibodies wherein the CH2 domain is replaced with an amino acid spacer that associate non-covalently to form tetravalent, dimeric antibody complexes, undue experimentation would be required to practice the claimed invention with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed invention and absent working examples providing evidence which is reasonably predictive that the claimed dimeric CH2 domain-deleted antibodies wherein the CH2 domain is replaced with an amino acid spacer effective non-covalently associate to form tetravalent, dimer antibody complexes, commensurate in scope with the claimed invention.

8. Claims 20, 29, 38-40, 63, 76-80 and 84-92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beresford et al (International Journal of Cancer, 81(6):911-917, 11 June 1999) in view of Kashmiri et al (WO 00/26394, 5/11/00) and Anderson et al (U.S. Patent 6,348,581 B1, priority at least to 2/18,1998, cited previously) and Thorpe et al (U.S. Patent 6,342,219 B1, 4/28/1999, cited previously).

The claims are drawn to a dimeric antibody that binds TAG-72 and comprises two antibodies that are non-covalently associated to form a tetravalent antibody dimer, wherein each of the antibodies in the dimer comprises two antibody heavy chain polypeptides and two antibody light chain polypeptides, wherein a CH2 domain is deleted from each of the four antibody heavy chain polypeptides in the dimeric antibody

and the dimeric antibody is a humanized antibody comprising the heavy chain variable region of SEQ ID NO:7 and the light chain variable region of SEQ ID NO:9 and each antibody in the dimeric antibody binds the same epitope and the antibody is conjugated to a cytotoxic agent. The claims are also drawn to a kit useful for the treatment of a mammal suffering from or predisposed to a neoplastic disorder, wherein the neoplastic disorder may be colon cancer, the kit comprising said dimeric antibody that binds TAG-72 and a label or insert indicating that said dimeric antibody may be used to treat neoplastic disorder. The intended use of the claimed kit for the treatment of a mammal suffering from or predisposed to a neoplastic disorder, wherein the neoplastic disorder may be colon cancer is given no patentable weight (MPEP 2111.03).

Beresford et al teach a CC49 scFv antibody dimer that binds TAG-72, wherein each scFv is dimeric comprising two repeating chains of VL and VH (i.e., VL-L-VH-L-VL-L-VH; each antibody in the dimer comprises two antibody heavy chains and two antibody light chains), wherein the two divalent antibodies non-covalently associate and lack a CH2 domain and is radiolabeled with ^{125}I or ^{131}I (see entire document, especially page 911, right column and page 912, left column). Beresford et al teach that the dimeric antibody has the advantages of rapid blood clearance, low kidney uptake and small size suitable for rapid penetration through tumor tissue, and increased tumor targeting, probably due to its increased functional affinity attributable to its multivalency make the dimeric CC49 scFv a strong candidate for imaging and therapeutic applications (see abstract and pages 915-916). Beresford et al do not specifically teach the humanized CC49 VH and VL sequences (SEQ ID Nos:7 and 9, respectively)

or conjugating the dimeric antibody to the recited cytotoxic agents. These deficiencies are made up for in the teachings of Kashmiri et al and Anderson et al and Thorpe et al.

Kashmiri et al teach the humanized CC49 VH (SEQ ID NO:7) and VL (SEQ ID NO:9) sequences that are less immunogenic in humans compared to their mouse counterparts (see entire document, especially Figure 11) (see the alignment attached to the back of this Office Action; Exhibits A-B).

Anderson et al teach humanized antibodies that bind TAG-72 and humanized antibodies are advantageous over murine antibodies because they have reduced immunogenicity (i.e., reduced HAMA response) in human patients (see column 8, lines 18-44). Anderson also teaches that the antibodies may be conjugated with various cytotoxic agents such as pseudomonas endotoxin, ricin, abrin, methotrexate, daunorubicin, doxorubicin and anti-proliferative agents (see column 15, lines 22-39).

Thorpe et al teach antibody conjugates for cancer therapy comprising anti-tumor drugs, cytokines, antimetabolites, alkylating agents, hormones, toxins, prodrugs and chemotherapeutic agents (see columns 75-76, 88-90, 113-118 and 125-127).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a humanized anti-TAG-72 scFv tetravalent antibody dimer comprising the humanized CC49 variable region sequences of Kashmiri et al and to have conjugated the scFv dimeric antibody to the various cytotoxic agents taught by Anderson et al and Thorpe et al for therapeutic benefit in cancer patients.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced a humanized anti-TAG-72 scFv tetravalent antibody dimer comprising the humanized CC49 variable region sequences of SEQ ID Nos:7 and 9 and to have conjugated the scFv dimeric antibody to various cytotoxic agents for therapeutic benefit in cancer patients in view of Beresford et al and Kashmiri et al and Anderson et al and Thorpe et al because Beresford et al teach a radiolabeled CC49 scFv antibody dimer that binds TAG-72, wherein each scFv is dimeric comprising two repeating chains of VL and VH (i.e., VL-L-VH-L-VL-L-VH; each antibody in the dimer comprises two antibody heavy chains and two antibody light chains), wherein the two divalent antibodies non-covalently associate and lack a CH2 domain and the dimeric antibody has the advantages of rapid blood clearance, low kidney uptake and increased tumor targeting, which make this dimeric CC49 scFv a strong candidate for imaging and therapeutic applications and Kashmiri et al teach the humanized CC49 variable region sequences of SEQ ID Nos:7 and 9 and both Kashmiri et al and Anderson et al teach that humanized CC49 antibodies are less immunogenic in human patients relative to murine antibodies (i.e., reduced HAMA response) and hence, better suited for human therapy. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced a humanized anti-TAG-72 scFv tetravalent antibody dimer comprising the humanized CC49 variable region sequences of SEQ ID Nos:7 and 9, conjugated to various cytotoxic agents for therapeutic benefit in cancer patients in view of Beresford et

al and Kashmiri et al and Anderson et al and Thorpe et al because Anderson et al and Thorpe et al teach various antibody conjugates comprising a cytotoxic agent for cancer immunotherapy. Therefore, one of ordinary skill in the art would have been motivated and had a reasonable expectation of success to humanize the scFv CC49 dimeric antibody of Beresford et al with the humanized CC49 variable region sequences of Kashmiri et al to reduce HAMA responses in human cancer patients and one of ordinary skill in the art would have been motivated to do so because the scFv CC49 dimeric antibody of Beresford et al has a rapid blood clearance, low kidney uptake, rapid penetration through tumor tissue, and demonstrates increased tumor targeting. Thus, a humanized dimeric CC49 scFv has distinct advantages over murine, monovalent antibodies for selectively delivering various cytotoxic agents conjugated to the antibody for immunotherapy in cancer patients. Thus, it would have been obvious to one skilled in the art at the time the invention was made to have produced a humanized anti-TAG-72 scFv tetravalent antibody dimer comprising the humanized CC49 variable region sequences of SEQ ID Nos:7 and 9, respectively and to have conjugated the scFv dimeric antibody to various cytotoxic agents for therapeutic benefit in cancer patients in view of Beresford et al and Kashmiri et al and Anderson et al and Thorpe et al.

Although the claims recite a kit, no positive recitation of the kit ingredients/elements distinguishes the claim over the references. Therefore, the references read on the claimed kit. Applicant is reminded that the intended use of the claimed kit for treating a mammal suffering from or predisposed to a neoplastic disorder, wherein the neoplastic disorder is colon cancer is given no patentable weight (MPEP

2111.03). It is further noted that the written material in the instructions is not considered to be within the statutory classes and does not carry patentable weight. See MPEP 706.03(a).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

9. Claims 20, 29, 38-40, 55-56, 62-63, 68-69, 75-82 and 84-92 under 35 U.S.C. 103(a) as being unpatentable over Gillies et al (Human Antibodies and Hybridomas, 1(1):47-54, 1990, cited previously) as evidenced by the specification in view of Kashmiri et al (WO 00/26394, 5/11/00) and Anderson et al (U.S. Patent 6,348,581 B1, priority at least to 2/18/1998, cited previously) and Thorpe et al (U.S. Patent 6,342,219 B1, 4/28/1999, cited previously).

Claims 20, 29, 38-40, 63, 76-80 and 84-92 have been described supra.

Claims 55-56, 62, 68-69, 75 and 81-82 recite wherein the dimeric antibody is a chimeric antibody, which is being interpreted as the humanized antibody in view of the indefinite nature of the claims (see 112, 2nd above) and wherein the CH3 domain is fused directly to the hinge region.

Gillies et al teach a CH2 domain deleted antibody that specifically binds TAG-72 (i.e., B72.3 antibody) wherein the CH3 domain (human CH3) is fused directly to the hinge region (see page 49, right column and page 48) and would necessarily exist as a dimeric antibody wherein two of the antibodies are non-covalently associated as evidenced by the specification. As evidenced by the specification at page 7 and

Example 1 (hinge directly fused to the CH3 domain), modified antibodies in which the CH2 region has been deleted and the hinge is directly fused to the CH3 domain spontaneously assemble to form stable tetravalent antibodies held together by non-covalent interactions. Gillies et al teach that the CH2 domain deleted antibody had increased binding activity and a shorter half-life in vivo and little ADCC activity and no CDC activity, which make this antibody useful for *in vivo* imaging of tumor, where the loss of effector functions (e.g., Fc receptor binding) is desired (see abstract and pages 52-54). (see Figure 1 and page 52, left column). Gillies et al do not specifically teach teach the humanized CC49 variable region sequences (SEQ ID Nos:7 and 9, respectively) or conjugating the dimeric antibody to the recited cytotoxic agents. These deficiencies are made up for in the teachings of Kashmiri et al and Anderson et al and Thorpe et al.

Kashmiri et al have been described supra.

Anderson et al have been described supra.

Thorpe et al have been described supra.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a humanized anti-TAG-72 CH2 domain deleted antibody wherein the CH3 domain is directly fused to the hinge region and comprising the humanized CC49 variable region sequences of Kashmiri et al and to have conjugated the anti-TAG-72 CH2 domain deleted antibody to various cytotoxic agents as taught by Anderson et al and Thorpe et al for therapeutic benefit in cancer patients.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced a humanized anti-TAG-72 tetravalent antibody dimer comprising the humanized CC49 variable region sequences of SEQ ID Nos:7 and 9 and to have conjugated the dimeric antibody to the various cytotoxic agents for therapeutic benefit in cancer patients in view of Gillies et al as evidenced by the specification and Kashmiri et al and Anderson et al and Thorpe et al because Gillies et al teach a CH2 domain deleted antibody that specifically binds TAG-72 (B72.3 antibody) wherein the CH3 domain is fused directly to the hinge region and would necessarily exist as a dimeric antibody wherein two of the antibodies non-covalently associate as evidenced by the specification, which shows that direct fusion of the hinge and CH3 domain in CH2 domain-deleted antibodies spontaneously assemble to form stable tetravalent antibodies held together by non covalent interactions (see page 7) and Kashmiri et al teach an anti-TAG-72 specific humanized CC49 antibody comprising the variable region sequences of SEQ ID Nos:7 and 9 and both Kashmiri et al and Anderson et al teach that humanized CC49 antibodies are less immunogenic in human patients relative to murine antibodies (i.e., reduced human anti-mouse antibody (HAMA) response) and hence, better suited for human therapy. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success at the time the invention was made to have produced a humanized anti-TAG-72 tetravalent antibody dimer comprising the humanized CC49 variable region sequences of SEQ ID Nos:7 and 9, conjugated to various cytotoxic agents for therapeutic benefit in cancer patients in

view of Gillies et al as evidenced by the specification and Kashmiri et al and Anderson et al and Thorpe et al because Anderson et al and Thorpe et al teach various antibody conjugates comprising a cytotoxic agent for cancer immunotherapy. Therefore, one of ordinary skill in the art would have been motivated and had a reasonable expectation of success at the time the invention was made to use the humanized CC49 variable region sequences of Kashmiri et al in the CH2 domain deleted antibody of Gillies et al to reduce HAMA responses in human cancer patients, reduce or eliminate antibody functions (i.e., ADCC and CDC) and increase the antigen-binding activity, thereby enhancing the therapeutic index of the antibody as a targeting element when conjugated to various cytotoxic agents. Further, as evidenced by the teachings of Anderson et al and Thorpe et al, it was known and routine in the art at the time the invention was made to conjugate an antibody with a cytotoxic agent for immunotherapy. Thus, it would have been obvious to one skilled in the art at the time the invention was made to have produced a humanized anti-TAG-72 tetravalent antibody dimer comprising the humanized CC49 variable region sequences of SEQ ID Nos:7 and 9 and to have conjugated the dimeric antibody to the various cytotoxic agents for therapeutic benefit in cancer patients in view of Gillies et al as evidenced by the specification and Kashmiri et al and Anderson et al and Thorpe et al.

Therefore, it is the Examiner's position that Gillies et al as evidenced by the specification and Kashmiri et al and Anderson et al and Thorpe et al have produced a humanized TAG-72 specific CH2 domain deleted antibody wherein the CH3 domain is directly fused to the hinge region that is identical to the claimed humanized TAG-72

specific CH2 domain deleted antibody also having the CH3 domain directly fused to the hinge region. One of ordinary skill in the art would reasonably conclude that the CH-2 domain deleted antibody of Gillies et al as evidenced by the specification and Kashmiri et al and Anderson et al and Thorpe et al also possesses the same structural and functional properties as those of the CH2 domain deleted antibodies claimed and, therefore, it appears that Gillies et al as evidenced by the specification and Kashmiri et al and Anderson et al and Thorpe et al have produced antibodies that are identical to the claimed antibodies. Since the Patent and Trademark Office does not have the facilities for examining and comparing the claimed antibodies with the antibodies of Gillies et al as evidenced by the specification and Kashmiri et al and Anderson et al and Thorpe et al, the burden of proof is upon the Applicants to show an unobvious distinction between the structural and functional characteristics of the claimed antibodies and the antibodies of the prior art. See In re Best, 562 F.2d 1252, 195 U.S.P.Q. 430 (CCPA 197) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Although the claims recite a kit, no positive recitation of the kit ingredients/elements distinguishes the claim over the references. Therefore, the references read on the claimed kit. Applicant is reminded that the intended use of the claimed kit for treating a mammal suffering from or predisposed to a neoplastic disorder, wherein the neoplastic disorder is colon cancer is given no patentable weight (MPEP 2111.03). It is further noted that the written material in the instructions is not considered

to be within the statutory classes and does not carry patentable weight. See MPEP 706.03(a).

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

10. No claim is allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Blanchard whose telephone number is (571) 272-0827. The examiner can normally be reached at Monday through Friday from 8:00 AM to 6:00 PM, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached at (571) 272-0832. The official fax number for the organization where this application or proceeding is assigned is 571-273-8300. Any inquiry of a general nature, matching or filed papers or relating to the status of this application or proceeding should be directed to Tony Parks for Art Unit 1643 whose telephone number is 571-272-0543.

Information regarding the status of an application may be obtained from the patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should

you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,
David J. Blanchard
571-272-0827

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER
4/23/04

99	533.5	88.2	284	7	ADG46862	Adg46862 Hum4VL-1i
100	530.5	87.7	284	2	AAR38321	Aar38321 Sequence

ALIGNMENTS

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RESULT 1
AAY95244
ID   AAY95244 standard; protein; 115 AA.
XX
AC   AAY95244;
XX
DT   12-SEP-2003  (revised)
DT   29-AUG-2000  (first entry)
XX
DE   Humanised antibody HuCC49 heavy chain variable region.
XX
KW   Humanised antibody; monoclonal antibody; CC49; HuCC49; CDR;
KW   complementarity determining region; mouse; human; carcinoma;
KW   colon cancer; tumor associated glycoprotein-72; TAG-72; tumour marker;
KW   diagnosis; therapy.
XX
OS   Mus musculus.
OS   Homo sapiens.
OS   Chimeric.
XX
FH   Key             Location/Qualifiers
FT   Region          31. .35
FT                   /note= "CDR1"
FT   Region          50. .67
FT                   /note= "CDR2"
FT   Region          99. .104
FT                   /note= "CDR3"
XX
PN   WO200026394-A1.
XX
PD   11-MAY-2000.
XX
PF   29-OCT-1999;   99WO-US025552.
XX
PR   31-OCT-1998;   98US-0106534P.
PR   02-NOV-1998;   98US-0106757P.
XX
PA   (USSH ) US DEPT HEALTH & HUMAN SERVICES.
XX
PI   Kashmiri SVS,  Padlan EA,  Schlom J;
XX
DR   WPI; 2000-365637/31.
XX
PT   Chimeric variants of CC49 monoclonal antibodies useful for detecting and
PT   treating cancers associated with the expression of the pancarcinoma tumor
PT   -associated antigen TAG-72.
XX
PS   Disclosure; Fig 4; 76pp; English.
XX
CC   The present sequence is that of the heavy chain variable region (VH) of
CC   huCC49, a humanised monoclonal antibody (MAb) formed by grafting
CC   hypervariable regions from murine MAb CC49 into VL and VH frameworks of
CC   human MAbs LEN and 21/28' CL, respectively, while retaining murine
CC   framework residues required for integrity of the antigen combining site
CC   structure. HuCC49 binds to the human pancarcinoma tumor associated
CC   glycoprotein-72 (TAG-72), which is found on the surface of certain human
CC   tumours. The invention is directed towards mouse-human chimeric variants
CC   of CC49 MAbs with minimal murine content, to methods of making such
CC   variants, and their therapeutic application. The invention provides
CC   complementarity determining region (CDR) variants of huCC49 in which
CC   fewer than all 6 CDRs of CC49 are present, and specificity determining
CC   region (SDR) variants of huCC49 in which only SDRs of at least 1 CDR from
CC   CC49 are present. Particular variants of HuCC9 have either L-CDR1 and/or
CC   L-CDR2 from human MAb LEN. These variants have the same or 2-fold lower
CC   affinity constant than HuCC49. Other variants additionally have
CC   corresponding human residues at position 97 of L-CDR3, and positions 60,
CC   61, 62 and 64 of H-CDR2, or have residues 31, 32 and 34 of H-CDR1 from a
CC   non-human anti-TAG-12 antibody. The variants are used in claimed methods
CC   of treating cancer and for detecting cancer cells that express TAG-72.
CC   (Updated on 12-SEP-2003 to standardise OS field)
XX
SQ   Sequence 115 AA;

  Query Match           100.0%;  Score 605;  DB 3;  Length 115;
  Best Local Similarity  100.0%;  Pred. No. 5.8e-47;
  Matches  115;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 QVQLVQSGAEVVKPGASVKISCKASGYTFTDHAIHWVKQNPGQRLEWIGYFSPGNDDFKY 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 QVQLVQSGAEVVKPGASVKISCKASGYTFTDHAIHWVKQNPGQRLEWIGYFSPGNDDFKY 60

Qy         61 NERFKGKATLTADTSASTAYVELSSLRSEDTAVYFCTRSLNMAYWGQGTLVTVSS 115
              |||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 NERFKGKATLTADTSASTAYVELSSLRSEDTAVYFCTRSLNMAYWGQGTLVTVSS 115
```

Exhibit A

99	536	90.5	284	2	AAY50694	Aay50694 Plasmid p
100	536	90.5	284	2	AAY57185	Aay57185 Amino aci

ALIGNMENTS

RESULT 1
AAY95243
ID AAY95243 standard; protein; 137 AA.
XX
AC AAY95243;
XX
DT 12-SEP-2003 (revised)
DT 29-AUG-2000 (first entry)
XX
DE Humanised antibody HuCC49 light chain variable region.
XX
KW Humanised antibody; monoclonal antibody; CC49; HuCC49; CDR;
KW complementarity determining region; mouse; human; carcinoma;
KW colon cancer; tumor associated glycoprotein-72; TAG-72; tumour marker;
KW diagnosis; therapy.
XX
OS Mus musculus.
OS Homo sapiens.
OS Chimeric.
XX
FH Key Location/Qualifiers
FT Region 44. .59
FT /note= "CDR1"
FT Region 76. .82
FT /note= "CDR2"
FT Region 115. .123
FT /note= "CDR3"
XX
PN WO200026394-A1.
XX
PD 11-MAY-2000.
XX
PF 29-OCT-1999; 99WO-US025552.
XX
PR 31-OCT-1998; 98US-0106534P.
PR 02-NOV-1998; 98US-0106757P.
XX
PA (USSH) US DEPT HEALTH & HUMAN SERVICES.
XX
PI Kashmiri SVS, Padlan EA, Schlom J;
XX
DR WPI; 2000-365637/31.
XX
PT Chimeric variants of CC49 monoclonal antibodies useful for detecting and
PT treating cancers associated with the expression of the pancarcinoma tumor
PT -associated antigen TAG-72.
XX
PS Disclosure; Fig 4; 76pp; English.
XX
CC The present sequence is that of the light chain variable region (VL) of
CC huCC49, a humanised monoclonal antibody (MAb) formed by grafting
CC hypervariable regions from murine MAb CC49 into VL and VH frameworks of
CC human MAbs LEN and 21/28' CL, respectively, while retaining murine
CC framework residues required for integrity of the antigen combining site
CC structure. HuCC49 binds to the human pancarcinoma tumor associated
CC glycoprotein-72 (TAG-72), which is found on the surface of certain human
CC tumours. The invention is directed towards mouse-human chimeric variants
CC of CC49 MAbs with minimal murine content, to methods of making such
CC variants, and their therapeutic application. The invention provides
CC complementarity determining region (CDR) variants of huCC49 in which
CC fewer than all 6 CDRs of CC49 are present, and specificity determining
CC region (SDR) variants of huCC49 in which only SDRs of at least 1 CDR from
CC CC49 are present. Particular variants of HuCC9 have either L-CDR1 and/or
CC L-CDR2 from human MAb LEN. These variants have the same or 2-fold lower
CC affinity constant than HuCC49. Other variants additionally have
CC corresponding human residues at position 97 of L-CDR3, and positions 60,
CC 61, 62 and 64 of H-CDR2. The variants are used in claimed methods of
CC treating cancer and for detecting cancer cells that express TAG-72.
CC (Updated on 12-SEP-2003 to standardise OS field)
XX
SQ Sequence 137 AA;

Query Match 100.0%; Score 592; DB 3; Length 137;
Best Local Similarity 100.0%; Pred. No. 4.3e-41;
Matches 114; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

```
Qy          1 DIVMSQSPDSLAVSLGERVTLNCKSSQSLLYSGNQKNYLAWYQQKPGQSPKLLIYWASAR 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         21 DIVMSQSPDSLAVSLGERVTLNCKSSQSLLYSGNQKNYLAWYQQKPGQSPKLLIYWASAR 80

Qy         61 ESGVPDRFSGSGSGTDFTLTISSVQAEDVAVYYCQQYYSYPLTFGAGTKLELKR 114
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         81 ESGVPDRFSGSGSGTDFTLTISSVQAEDVAVYYCQQYYSYPLTFGAGTKLELKR 134
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AA.

Exhibit B